

REMARKS

Claims 1 to 17 are pending in the application. Claims 11 to 17 have been withdrawn as a result of an earlier restriction requirement. Claims 4 to 6, 8 and 9 have been canceled. Claims 1 to 3, 7 and 10 remain in this application.

With respect to the amendment to the specification herein submitted, the Applicant submits that the section entitled "cross-reference to related applications" had not been previously included in the application as a result of a clerical error. This amendment is made in the purpose of correcting this clerical error.

With respect to the scope of enablement rejection of claims 1-10 under 35 USC §112, first paragraph, reconsideration by the Examiner is respectfully requested on the following grounds; Claim 1 has been amended to refer solely to the Taq and Vent_r® polymerases as DNA polymerases, and to 1-propanol as the alcohol. Claim 10 has been amended accordingly. Claims 4-6, 8 and 9 have been canceled as a result of this amendment.

Regarding the applicability of the claimed method to any DNA template and to standard reaction conditions, the Applicant would like to submit the following argumentation. Other mutagenic PCR methods (error prone PCR) have been reported in the past (each with its own set of features). Using either salts or highly different concentrations of one individual dNTP (triphosphorylated nucleotide) compared to the three others, it has been shown to decrease the fidelity of polymerases in order to achieve random mutations. It is well known in the art that these methods can be used on any gene or DNA with the same efficiency, since error prone PCR has already been used with a

large number of unrelated genes (see herein enclosed references in the PTO form SB08 for example: Cadwell and Joyce (1992) PCR Methods and Appl., 2: 28-33; Keefe and Szostak, Nature, vol. 410, p. 715, 2001; Chiang et al., PCR Methods and Applications, vol 2, p. 210, 1993; Huang et al., DNA and Cell Biology, vol. 15, p. 589, 1996; Keohavong et al., PCR Methods and Applications, vol. 2, p. 288, 1993). By opposition to DNA shuffling methods, the efficiency of error prone PCR methods is not sensitive to individual DNA sequences. This is explained by the fact that DNA shuffling methods involve recombination events among homologous fragments, rather than polymerase-induced random mutations like the present method.

As further argument, the Applicant wishes to submit to the Examiner the herein enclosed signed declaration of Marc Beauregard, Ph.D. Exhibit B of this declaration clearly shows a different gene (*axeA*) present a similar amplification yield, mutation rate, deletion rate and mutational bias to those of MB-1 as disclosed in the example section of the present application. Those two genes have nucleotide sequences sharing less than 20% identity, confirming that the method of the present application is producing a constant mutation profile when applied to different DNA templates. The content of this declaration, combined with the exemplification of the use of both Taq and Vent[®] polymerases and 1-propanol in the present application, is believed by the Applicant to overcome the scope of enablement rejection of claims 1-3, 7 and 10 as amended.

With respect to the written description rejection of claims 1-10 under 35 USC §112, first paragraph, it is believed that this rejection is overcome by the above amendment. The restriction of the claims to Taq and Vent[®] polymerases as DNA polymerases, and 1-propanol as the alcohol, combined with the exemplification of those

polymerases and alcohol in the present application (pages 17-27), is believed to provide adequate support necessary to the skilled artisan to practice the claimed subject matter. Regarding the applicability of the claimed method to any DNA template, the Applicant believes that the previous argumentation and the herein enclosed declaration provides sufficient proof for allowance of the use of the present method on any DNA templates. It is therefore respectfully submitted that the present claims, as amended, are applicable to any DNA template and should be allowed as such.

With respect of the rejection of claims 1-10 under 35 USC §112, second paragraph, reconsideration by the Examiner is respectfully requested on the following grounds;

Claim 1 has been amended to replace the expression "in concentration sufficient to lower the fidelity of said DNA polymerase and causing mutagenesis during said polymerization reaction" as to now claim "in a concentration of between 0.1% to 15%". The support for this amendment can be found in paragraph [0061]. The rejection of claim 1 under 35 USC §112, second paragraph, is therefore believed to be overcome by this amendment.

Claim 1 has been further rejected for the expression "to lower the fidelity of said DNA polymerase". This rejection is now moot as a result of an amendment submitted above.

Claim 10 has been amended to replace the expression "conditions that allow for controlling mutational bias" with the expression "conditions that allow for the induction of a random mutation". The Applicant respectfully submits to the Examiner that the "conditions" claimed in claim 10 will be understood by the skilled artisan as being

applicable to the composition in order to allow the induction of random mutations. Examples of such conditions allowing the induction of random mutations are described in paragraphs [0048] (use of unequal amounts of dNTPs) and [0049] (use of a melting point reducing agent) of the present application. Therefore, the Applicant respectfully submits that the present amendment is sufficient to overcome the rejection of claim 10.

Claim 2 has been amended as to replace the expression "said mutation" with the expression "said random mutation", thus overcoming the rejection of the Examiner for insufficient antecedent basis.

Claim 7 has been amended as to now read "The method of claim 1, wherein a mutated nucleic acid sequence is obtained, said mutated nucleic acid sequence encoding for a biologically active protein". This amendment is believed to overcome the rejection of claim 7 for insufficient antecedent basis .

The Applicant submits that no new matter has been added by the present amendments.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 1-3, 7 and 10 at an early date is solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

A fee of \$510.00 for a small entity is necessitated by this response as the payment for the three-month extension of time for reply. The Commissioner is hereby authorized to charge this amount to Deposit Account No. 19-5113. No additional fees are

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believed to be necessitated by this amendment. However, should this be an error, authorization is hereby give to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

Respectfully submitted,

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Enclosures Declaration by Marc Beauregard, Ph.D.
Information Disclosure Statement